A toolkit for quantification of biological age from blood-chemistry and organ-function-test data: BioAge

Dayoon Kwon, MPH[1,2]; Daniel W. Belsky[2,3]

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, 90095, USA
[2]Robert N. Butler Columbia Aging Center, Mailman School of Public Health, Columbia University, New York, NY, 10032, USA
[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, 10032, USA

Supplementary Information

I. Analysis of the NHANES IV data using the BioAge package

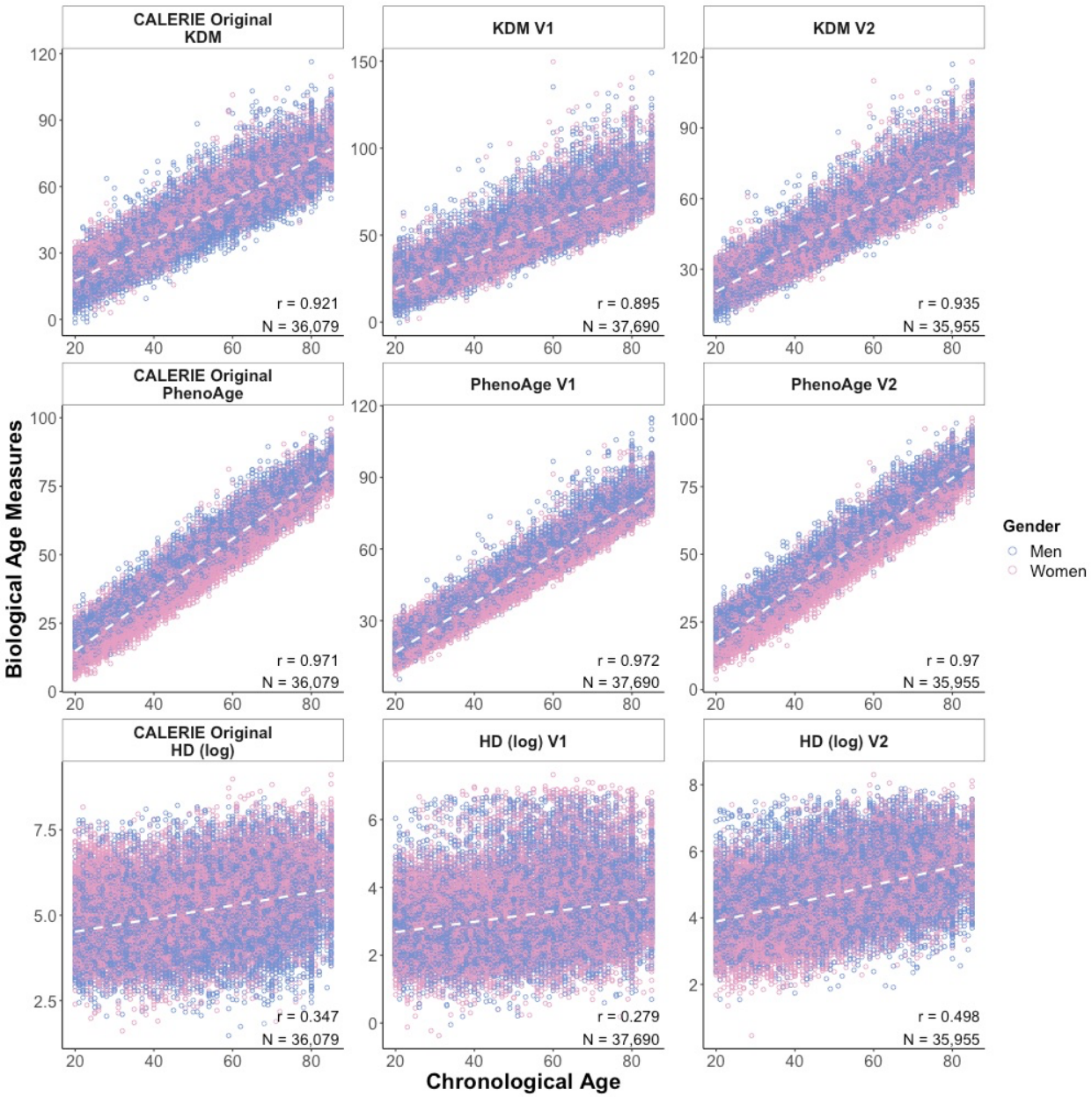


Fig s1.1 KDM, PhenoAge, and HD biological aging measures plotted against chronological age for participants in the NHANES IV

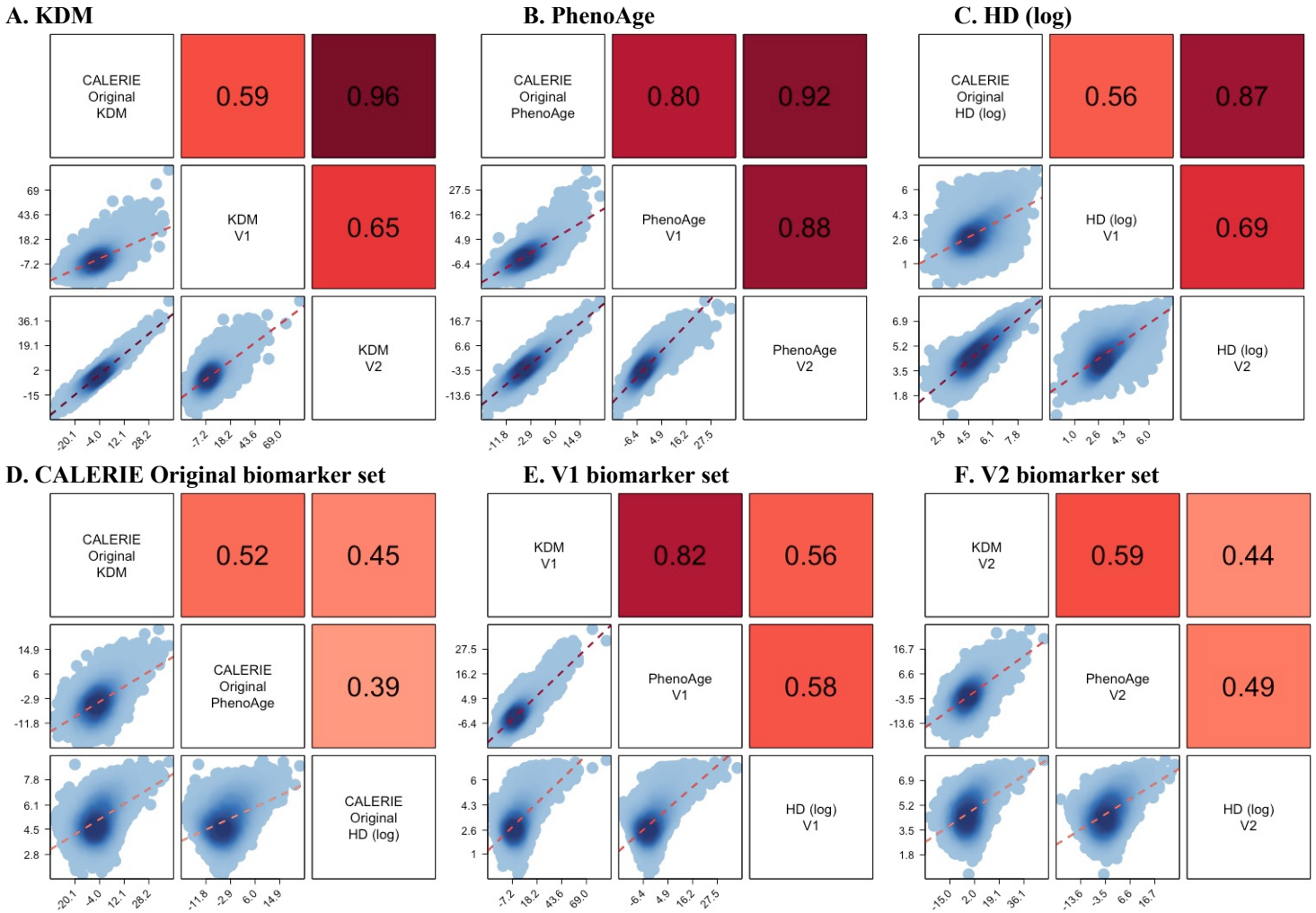


Fig s1.2 A matrix of association plots among KDM, PhenoAge, and HD biological aging measures in the NHANES IV

Tab s1.1 Associations of biological aging measures with mortality in the NHANES IV

	Original		CALERIE Original			V1			V2		
	KDM	PhenoAge	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)
	Hazard Ratio (95% CI)										
Full Sample											
n	8,234	27,837	26,688	26,688	26,688	27,904	27,904	27,904	26,580	26,580	26,580
BA	1.36 (1.2, 1.55)	1.47 (1.42, 1.51)	1.24 (1.2, 1.29)	1.39 (1.34, 1.45)	1.33 (1.28, 1.39)	1.35 (1.3, 1.39)	1.39 (1.34, 1.43)	1.39 (1.34, 1.44)	1.26 (1.22, 1.31)	1.43 (1.37, 1.49)	1.44 (1.38, 1.51)
Stratified by Gender											
Men											
n	4,114	13,421	12,907	12,907	12,907	13,453	13,453	13,453	12,879	12,879	12,879
BA	1.44 (1.23, 1.69)	1.44 (1.38, 1.5)	1.26 (1.2, 1.32)	1.38 (1.31, 1.45)	1.3 (1.24, 1.37)	1.37 (1.31, 1.43)	1.35 (1.29, 1.41)	1.37 (1.31, 1.44)	1.28 (1.22, 1.34)	1.41 (1.34, 1.49)	1.4 (1.32, 1.49)
Women											
n	4,120	14,416	13,781	13,781	13,781	14,451	14,451	14,451	13,701	13,701	13,701
BA	1.23 (0.98, 1.54)	1.52 (1.45, 1.6)	1.22 (1.15, 1.3)	1.41 (1.32, 1.5)	1.38 (1.28, 1.48)	1.32 (1.26, 1.38)	1.46 (1.38, 1.53)	1.41 (1.34, 1.49)	1.24 (1.18, 1.31)	1.46 (1.37, 1.55)	1.53 (1.41, 1.66)
Stratified by Race											
White											
n	3,937	13,958	13,486	13,486	13,486	13,984	13,984	13,984	13,447	13,447	13,447
BA	1.44 (1.21, 1.72)	1.54 (1.47, 1.6)	1.27 (1.21, 1.33)	1.47 (1.39, 1.55)	1.34 (1.27, 1.42)	1.39 (1.33, 1.45)	1.44 (1.38, 1.51)	1.47 (1.4, 1.54)	1.28 (1.22, 1.34)	1.49 (1.42, 1.58)	1.52 (1.43, 1.63)
Black											
n	1,467	5,176	4,887	4,887	4,887	5,201	5,201	5,201	4,851	4,851	4,851
BA	1.51 (1.15, 1.99)	1.37 (1.28, 1.47)	1.21 (1.12, 1.31)	1.3 (1.19, 1.42)	1.4 (1.27, 1.55)	1.3 (1.22, 1.38)	1.31 (1.22, 1.39)	1.32 (1.21, 1.44)	1.26 (1.17, 1.35)	1.36 (1.26, 1.48)	1.47 (1.31, 1.64)
Other											
n	2,830	8,703	8,315	8,315	8,315	8,719	8,719	8,719	8,282	8,282	8,282
BA	1.21 (0.89, 1.65)	1.37 (1.28, 1.48)	1.18 (1.09, 1.28)	1.25 (1.14, 1.36)	1.22 (1.12, 1.34)	1.27 (1.19, 1.36)	1.32 (1.22, 1.42)	1.27 (1.18, 1.37)	1.19 (1.1, 1.29)	1.3 (1.19, 1.42)	1.27 (1.15, 1.4)
People Aged 65 and Younger											
≤65 years											
n	6,915	21,252	20,430	20,430	20,430	21,292	21,292	21,292	20,344	20,344	20,344
BA	1.27 (1.06, 1.53)	1.61 (1.52, 1.7)	1.29 (1.21, 1.39)	1.47 (1.38, 1.58)	1.45 (1.34, 1.56)	1.46 (1.39, 1.54)	1.51 (1.43, 1.6)	1.49 (1.4, 1.58)	1.34 (1.25, 1.44)	1.51 (1.41, 1.61)	1.54 (1.42, 1.67)

KDM = Klemera-Doubal method, HD = homeostatic dysregulation, CI = confidence interval, BA = biological age. BA coefficients in the table are hazard ratios estimated from Cox proportional hazard regressions. KDM and PhenoAge measures were differenced from chronological age for analysis. These differenced values were then standardized to

have M=0, SD=1 separately for men and women within the analysis sample so that effect-sizes are denominated in terms of a sex-specific 1 SD unit increase in BA advancement. The original KDM algorithm (left-most column) was projected onto data from NHANES 2007-2010 only because other NHANES IV waves did not include spirometry measurements. The original PhenoAge algorithm (second column from left) was projected onto data from NHANES 1999-2010 and 2015-2018 only because the intervening waves did not include CRP measurements

Tab s1.2 Associations of biological aging measures with healthspan-related characteristics in the NHANES IV

	Original		CALERIE Original			V1			V2		
	KDM	PhenoAge	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)
						b (95% CI)					
Full Sample											
SRH	0.25 (0.23, 0.27)	0.21 (0.2, 0.22)	0.16 (0.15, 0.17)	0.2 (0.19, 0.21)	0.15 (0.13, 0.16)	0.17 (0.16, 0.18)	0.16 (0.15, 0.17)	0.2 (0.19, 0.21)	0.15 (0.14, 0.16)	0.18 (0.17, 0.19)	0.23 (0.22, 0.24)
ADL	0.13 (0.1, 0.16)	0.17 (0.15, 0.19)	0.09 (0.07, 0.1)	0.14 (0.12, 0.15)	0.09 (0.08, 0.11)	0.14 (0.12, 0.15)	0.16 (0.14, 0.18)	0.13 (0.12, 0.15)	0.09 (0.08, 0.11)	0.14 (0.13, 0.16)	0.12 (0.11, 0.14)
Walk speed	-	0.21 (0.18, 0.24)	0.1 (0.08, 0.13)	0.16 (0.14, 0.19)	0.12 (0.09, 0.15)	0.16 (0.13, 0.18)	0.17 (0.14, 0.2)	0.18 (0.15, 0.2)	0.1 (0.07, 0.12)	0.15 (0.12, 0.18)	0.17 (0.14, 0.2)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Stratified by Gender											
Men											
SRH	0.23 (0.2, 0.26)	0.22 (0.2, 0.23)	0.17 (0.15, 0.19)	0.19 (0.17, 0.21)	0.16 (0.14, 0.18)	0.18 (0.16, 0.19)	0.17 (0.15, 0.19)	0.19 (0.17, 0.2)	0.17 (0.15, 0.18)	0.18 (0.17, 0.2)	0.22 (0.2, 0.24)
ADL	0.12 (0.08, 0.15)	0.15 (0.13, 0.17)	0.09 (0.07, 0.11)	0.12 (0.1, 0.14)	0.08 (0.06, 0.1)	0.15 (0.13, 0.17)	0.15 (0.13, 0.17)	0.12 (0.1, 0.14)	0.1 (0.08, 0.12)	0.12 (0.1, 0.14)	0.1 (0.08, 0.13)
Walk speed	-	0.16 (0.12, 0.2)	0.09 (0.05, 0.12)	0.13 (0.09, 0.16)	0.11 (0.07, 0.14)	0.12 (0.09, 0.16)	0.11 (0.08, 0.15)	0.14 (0.11, 0.18)	0.08 (0.05, 0.12)	0.11 (0.07, 0.14)	0.14 (0.1, 0.18)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Women											
SRH	0.28 (0.25, 0.31)	0.22 (0.2, 0.23)	0.16 (0.14, 0.17)	0.21 (0.2, 0.23)	0.13 (0.11, 0.15)	0.16 (0.14, 0.17)	0.16 (0.14, 0.17)	0.21 (0.2, 0.23)	0.14 (0.12, 0.15)	0.17 (0.15, 0.19)	0.24 (0.23, 0.26)
ADL	0.14 (0.09, 0.19)	0.19 (0.17, 0.22)	0.08 (0.06, 0.1)	0.16 (0.13, 0.18)	0.1 (0.08, 0.13)	0.13 (0.11, 0.15)	0.18 (0.15, 0.2)	0.15 (0.13, 0.17)	0.08 (0.06, 0.11)	0.16 (0.14, 0.19)	0.16 (0.13, 0.19)
Walk speed	-	0.27 (0.22, 0.31)	0.12 (0.08, 0.16)	0.2 (0.16, 0.25)	0.13 (0.08, 0.18)	0.19 (0.15, 0.23)	0.23 (0.18, 0.27)	0.21 (0.17, 0.25)	0.11 (0.07, 0.15)	0.19 (0.14, 0.23)	0.21 (0.16, 0.26)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Stratified by Race											
White											
SRH	0.3 (0.27, 0.33)	0.27 (0.25, 0.28)	0.17 (0.15, 0.19)	0.26 (0.25, 0.28)	0.15 (0.14, 0.17)	0.21 (0.2, 0.23)	0.22 (0.21, 0.24)	0.21 (0.2, 0.23)	0.17 (0.15, 0.18)	0.25 (0.23, 0.26)	0.24 (0.23, 0.26)
ADL	0.15 (0.11, 0.19)	0.2 (0.18, 0.22)	0.09 (0.07, 0.11)	0.16 (0.14, 0.19)	0.1 (0.08, 0.12)	0.15 (0.13, 0.17)	0.18 (0.16, 0.2)	0.15 (0.13, 0.17)	0.1 (0.08, 0.12)	0.17 (0.15, 0.19)	0.13 (0.11, 0.16)
Walk speed	-	0.25 (0.21, 0.28)	0.12 (0.08, 0.15)	0.18 (0.15, 0.22)	0.12 (0.08, 0.16)	0.17 (0.13, 0.21)	0.2 (0.17, 0.24)	0.17 (0.13, 0.2)	0.12 (0.09, 0.15)	0.18 (0.15, 0.22)	0.16 (0.12, 0.2)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Black											

	Original		CALERIE Original			V1			V2		
	KDM	PhenoAge	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)
						b (95% CI)					
SRH	0.18 (0.13, 0.22)	0.17 (0.14, 0.19)	0.15 (0.13, 0.17)	0.17 (0.15, 0.2)	0.15 (0.13, 0.18)	0.14 (0.11, 0.16)	0.14 (0.12, 0.16)	0.17 (0.14, 0.19)	0.15 (0.13, 0.18)	0.16 (0.14, 0.18)	0.21 (0.18, 0.24)
ADL	0.08 (0, 0.16)	0.13 (0.1, 0.17)	0.07 (0.03, 0.11)	0.1 (0.06, 0.14)	0.1 (0.06, 0.14)	0.13 (0.1, 0.17)	0.14 (0.11, 0.17)	0.14 (0.1, 0.18)	0.08 (0.05, 0.12)	0.11 (0.08, 0.15)	0.12 (0.07, 0.17)
Walk speed	-	0.14 (0.07, 0.21)	0.02 (-0.05, 0.08)	0.08 (0.01, 0.16)	0.07 (-0.01, 0.15)	0.11 (0.05, 0.18)	0.13 (0.06, 0.19)	0.15 (0.07, 0.22)	0.03 (-0.03, 0.1)	0.1 (0.03, 0.17)	0.11 (0.02, 0.2)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Other											
SRH	0.15 (0.11, 0.19)	0.15 (0.13, 0.17)	0.12 (0.1, 0.14)	0.14 (0.13, 0.16)	0.11 (0.09, 0.13)	0.14 (0.12, 0.16)	0.14 (0.12, 0.15)	0.15 (0.13, 0.17)	0.11 (0.09, 0.13)	0.13 (0.11, 0.15)	0.17 (0.15, 0.19)
ADL	0.15 (0.09, 0.21)	0.15 (0.12, 0.18)	0.09 (0.06, 0.12)	0.14 (0.11, 0.17)	0.08 (0.05, 0.11)	0.13 (0.1, 0.16)	0.14 (0.11, 0.18)	0.11 (0.08, 0.14)	0.09 (0.06, 0.12)	0.12 (0.09, 0.15)	0.12 (0.08, 0.15)
Walk speed	-	0.15 (0.09, 0.21)	0.02 (-0.04, 0.07)	0.09 (0.04, 0.15)	0.04 (-0.01, 0.1)	0.11 (0.06, 0.16)	0.14 (0.09, 0.2)	0.11 (0.06, 0.17)	0.01 (-0.04, 0.07)	0.08 (0.03, 0.14)	0.07 (0.01, 0.14)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Stratified by Age											
Age 20-40											
SRH	0.21 (0.17, 0.25)	0.19 (0.17, 0.21)	0.15 (0.13, 0.17)	0.16 (0.14, 0.18)	0.07 (0.05, 0.09)	0.11 (0.09, 0.14)	0.09 (0.07, 0.12)	0.12 (0.09, 0.14)	0.15 (0.12, 0.17)	0.12 (0.1, 0.14)	0.15 (0.13, 0.18)
ADL	0.02 (-0.08, 0.13)	0.11 (0.06, 0.17)	0.03 (-0.03, 0.08)	0.07 (0.02, 0.13)	0.03 (-0.02, 0.08)	0.07 (0.02, 0.13)	0.08 (0.03, 0.13)	0.08 (0.02, 0.13)	0.04 (-0.02, 0.1)	0.07 (0.02, 0.12)	0.06 (0, 0.12)
Walk speed	-	-	-	-	-	-	-	-	-	-	-
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Age 40-60											
SRH	0.28 (0.25, 0.32)	0.26 (0.24, 0.28)	0.2 (0.18, 0.22)	0.24 (0.22, 0.26)	0.21 (0.19, 0.23)	0.22 (0.2, 0.24)	0.23 (0.21, 0.25)	0.24 (0.22, 0.26)	0.19 (0.17, 0.21)	0.22 (0.2, 0.24)	0.28 (0.26, 0.3)
ADL	0.18 (0.09, 0.27)	0.17 (0.12, 0.21)	0.09 (0.05, 0.14)	0.14 (0.1, 0.19)	0.14 (0.09, 0.19)	0.13 (0.08, 0.18)	0.14 (0.1, 0.19)	0.15 (0.11, 0.2)	0.09 (0.05, 0.14)	0.12 (0.08, 0.17)	0.17 (0.12, 0.22)
Walk speed	-	0.22 (0.17, 0.27)	0.15 (0.11, 0.2)	0.19 (0.14, 0.23)	0.18 (0.14, 0.23)	0.17 (0.13, 0.22)	0.18 (0.14, 0.23)	0.2 (0.16, 0.24)	0.15 (0.1, 0.19)	0.17 (0.13, 0.22)	0.22 (0.17, 0.26)
Grip strength	-	-	-	-	-	-	-	-	-	-	-
Age 60-80											
SRH	0.26 (0.22, 0.3)	0.21 (0.19, 0.23)	0.15 (0.13, 0.16)	0.21 (0.19, 0.23)	0.17 (0.15, 0.19)	0.17 (0.15, 0.18)	0.18 (0.16, 0.2)	0.22 (0.2, 0.24)	0.14 (0.12, 0.15)	0.2 (0.18, 0.22)	0.26 (0.24, 0.28)
ADL	0.11 (0.08, 0.15)	0.16 (0.14, 0.17)	0.09 (0.07, 0.11)	0.14 (0.12, 0.15)	0.09 (0.07, 0.1)	0.13 (0.12, 0.15)	0.15 (0.13, 0.16)	0.13 (0.11, 0.14)	0.09 (0.07, 0.11)	0.14 (0.12, 0.16)	0.12 (0.1, 0.15)
Walk speed	-	0.21	0.1	0.16	0.11	0.15	0.16	0.16	0.09	0.14	0.16

	Original		CALERIE Original			V1			V2		
	KDM	PhenoAge	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)
						b (95% CI)					
		(0.17, 0.25)	(0.06, 0.13)	(0.12, 0.19)	(0.07, 0.15)	(0.12, 0.19)	(0.12, 0.2)	(0.13, 0.2)	(0.06, 0.13)	(0.1, 0.18)	(0.12, 0.2)
Grip strength	-	-	-	-	-	-	-	-	-	-	-

KDM = Klemera-Doubal method, HD = homeostatic dysregulation, CI = confidence interval, SRH = self-rated health, ADL = activities of daily living. Coefficients are from linear regressions of healthspan-related characteristics on biological aging measures. Outcome variables were standardized to have M=0, SD=1 for analysis. Standardization was performed separately for men and women in the case of grip strength. Walk speed was log transformed prior to standardization to reduce skew. KDM and PhenoAge measures were differenced from chronological age for analysis (i.e. values = BA-CA). These differenced values were then standardized to have M=0, SD=1 separately for men and women within the analysis sample so that effect-sizes are denominated in terms of a sex-specific 1 SD unit increase in biological age advancement. Models included covariates for chronological age and sex. The original KDM algorithm (left-most column) was projected onto data from NHANES 2007-2010 only because other NHANES IV waves did not include spirometry measurements. The original PhenoAge algorithm (second column from left) was projected onto data from NHANES 1999-2010 and 2015-2018 only because the intervening waves did not include CRP measurements. Walk speed was measured only in NHANES 1999-2002 and is available only for participants aged 50 and older. Grip strength was measured only in NHANES 2011-2014

Tab s1.3 Associations of socioeconomic circumstances with biological aging measures in the NHANES IV

	Original		CALERIE Original			V1			V2		
	KDM	PhenoAge	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)
						b (95% CI)					
Full Sample											
Education	-0.19 (-0.22, -0.17)	-0.07 (-0.08, -0.06)	-0.08 (-0.09, -0.07)	-0.1 (-0.11, -0.09)	-0.1 (-0.11, -0.09)	-0.07 (-0.08, -0.06)	-0.07 (-0.08, -0.06)	-0.09 (-0.1, -0.08)	-0.07 (-0.08, -0.06)	-0.09 (-0.1, -0.07)	-0.11 (-0.12, -0.1)
Annual income	-0.17 (-0.19, -0.15)	-0.11 (-0.12, -0.1)	-0.07 (-0.08, -0.06)	-0.13 (-0.14, -0.12)	-0.12 (-0.13, -0.11)	-0.1 (-0.11, -0.09)	-0.1 (-0.11, -0.09)	-0.1 (-0.11, -0.09)	-0.08 (-0.09, -0.07)	-0.12 (-0.13, -0.11)	-0.11 (-0.12, -0.11)
Poverty ratio	-0.18 (-0.21, -0.16)	-0.14 (-0.15, -0.13)	-0.07 (-0.08, -0.06)	-0.13 (-0.14, -0.12)	-0.1 (-0.11, -0.09)	-0.09 (-0.1, -0.08)	-0.09 (-0.1, -0.08)	-0.11 (-0.12, -0.1)	-0.07 (-0.08, -0.06)	-0.11 (-0.12, -0.1)	-0.12 (-0.13, -0.11)
Stratified by Gender											
Men											
Education	-0.21 (-0.24, -0.18)	-0.08 (-0.09, -0.06)	-0.08 (-0.1, -0.07)	-0.1 (-0.11, -0.08)	-0.09 (-0.1, -0.07)	-0.07 (-0.09, -0.06)	-0.08 (-0.09, -0.06)	-0.07 (-0.09, -0.06)	-0.08 (-0.09, -0.06)	-0.09 (-0.11, -0.08)	-0.1 (-0.11, -0.09)
Annual income	-0.16 (-0.19, -0.13)	-0.1 (-0.11, -0.08)	-0.05 (-0.07, -0.03)	-0.11 (-0.12, -0.09)	-0.11 (-0.13, -0.1)	-0.09 (-0.11, -0.07)	-0.09 (-0.11, -0.08)	-0.09 (-0.1, -0.07)	-0.06 (-0.08, -0.05)	-0.11 (-0.13, -0.1)	-0.1 (-0.12, -0.09)
Poverty ratio	-0.18 (-0.21, -0.15)	-0.12 (-0.13, -0.1)	-0.07 (-0.08, -0.05)	-0.12 (-0.13, -0.1)	-0.1 (-0.12, -0.09)	-0.09 (-0.1, -0.07)	-0.09 (-0.1, -0.07)	-0.1 (-0.11, -0.08)	-0.07 (-0.08, -0.05)	-0.11 (-0.12, -0.09)	-0.11 (-0.12, -0.1)
Women											
Education	-0.18 (-0.21, -0.15)	-0.08 (-0.1, -0.07)	-0.07 (-0.09, -0.06)	-0.11 (-0.12, -0.09)	-0.1 (-0.12, -0.09)	-0.07 (-0.08, -0.05)	-0.08 (-0.09, -0.06)	-0.12 (-0.13, -0.1)	-0.06 (-0.08, -0.05)	-0.08 (-0.1, -0.07)	-0.12 (-0.13, -0.1)
Annual income	-0.18 (-0.21, -0.15)	-0.12 (-0.13, -0.11)	-0.08 (-0.1, -0.07)	-0.15 (-0.17, -0.14)	-0.12 (-0.14, -0.11)	-0.11 (-0.12, -0.09)	-0.11 (-0.13, -0.1)	-0.12 (-0.13, -0.11)	-0.09 (-0.1, -0.07)	-0.13 (-0.15, -0.12)	-0.12 (-0.14, -0.11)
Poverty ratio	-0.19 (-0.22, -0.16)	-0.15 (-0.17, -0.14)	-0.08 (-0.09, -0.06)	-0.15 (-0.16, -0.13)	-0.1 (-0.11, -0.08)	-0.09 (-0.1, -0.08)	-0.09 (-0.11, -0.08)	-0.13 (-0.15, -0.12)	-0.07 (-0.08, -0.05)	-0.11 (-0.13, -0.1)	-0.12 (-0.13, -0.11)
Stratified by Race											
White											
Education	-0.24 (-0.27, -0.21)	-0.14 (-0.15, -0.12)	-0.1 (-0.11, -0.08)	-0.19 (-0.21, -0.18)	-0.1 (-0.11, -0.08)	-0.12 (-0.13, -0.1)	-0.15 (-0.16, -0.13)	-0.1 (-0.12, -0.09)	-0.1 (-0.11, -0.08)	-0.17 (-0.19, -0.16)	-0.12 (-0.13, -0.1)
Annual income	-0.18 (-0.21, -0.15)	-0.14 (-0.16, -0.13)	-0.07 (-0.09, -0.06)	-0.18 (-0.19, -0.16)	-0.12 (-0.13, -0.1)	-0.11 (-0.13, -0.1)	-0.14 (-0.16, -0.13)	-0.11 (-0.12, -0.09)	-0.09 (-0.1, -0.07)	-0.17 (-0.18, -0.15)	-0.12 (-0.13, -0.11)
Poverty ratio	-0.19 (-0.21, -0.16)	-0.17 (-0.19, -0.16)	-0.08 (-0.09, -0.06)	-0.19 (-0.2, -0.17)	-0.1 (-0.11, -0.08)	-0.12 (-0.13, -0.1)	-0.14 (-0.16, -0.13)	-0.11 (-0.13, -0.1)	-0.08 (-0.1, -0.07)	-0.17 (-0.18, -0.15)	-0.11 (-0.13, -0.1)
Black											
Education	-0.11 (-0.17, -0.06)	-0.04 (-0.06, -0.01)	-0.03 (-0.05, 0)	-0.06 (-0.08, -0.03)	-0.09 (-0.11, -0.07)	-0.05 (-0.08, -0.03)	-0.06 (-0.09, -0.04)	-0.05 (-0.07, -0.02)	-0.05 (-0.08, -0.02)	-0.08 (-0.11, -0.05)	-0.06 (-0.08, -0.04)
Annual income	-0.12 (-0.18, -0.07)	-0.1 (-0.12, -0.07)	-0.07 (-0.1, -0.05)	-0.08 (-0.11, -0.06)	-0.12 (-0.14, -0.1)	-0.11 (-0.13, -0.08)	-0.1 (-0.13, -0.08)	-0.07 (-0.1, -0.05)	-0.1 (-0.13, -0.08)	-0.11 (-0.14, -0.09)	-0.08 (-0.1, -0.06)
Poverty ratio	-0.12 (-0.17, -0.06)	-0.14 (-0.16, -0.11)	-0.08 (-0.1, -0.05)	-0.1 (-0.12, -0.07)	-0.11 (-0.14, -0.09)	-0.09 (-0.12, -0.07)	-0.09 (-0.12, -0.07)	-0.08 (-0.1, -0.06)	-0.1 (-0.12, -0.07)	-0.11 (-0.14, -0.09)	-0.09 (-0.11, -0.07)
Other											
Education	-0.1 (-0.13, -0.07)	-0.02 (-0.03, 0)	-0.04 (-0.06, -0.03)	-0.04 (-0.06, -0.03)	-0.09 (-0.11, -0.08)	-0.05 (-0.07, -0.04)	-0.05 (-0.07, -0.03)	-0.07 (-0.08, -0.05)	-0.04 (-0.06, -0.03)	-0.05 (-0.07, -0.03)	-0.08 (-0.1, -0.07)

	Original		CALERIE Original			V1			V2		
	KDM	PhenoAge	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)	KDM	PhenoAge	HD (log)
						b (95% CI)					
Annual income	-0.09 (-0.13, -0.05)	-0.03 (-0.05, -0.02)	-0.02 (-0.04, -0.0002)	-0.07 (-0.09, -0.05)	-0.11 (-0.12, -0.09)	-0.07 (-0.09, -0.05)	-0.08 (-0.1, -0.06)	-0.08 (-0.09, -0.06)	-0.03 (-0.05, -0.02)	-0.09 (-0.1, -0.07)	-0.08 (-0.1, -0.06)
Poverty ratio	-0.11 (-0.15, -0.08)	-0.06 (-0.08, -0.05)	-0.02 (-0.04, -0.003)	-0.07 (-0.09, -0.05)	-0.09 (-0.11, -0.07)	-0.06 (-0.08, -0.04)	-0.07 (-0.09, -0.05)	-0.09 (-0.11, -0.07)	-0.02 (-0.04, -0.01)	-0.07 (-0.09, -0.05)	-0.08 (-0.1, -0.06)
Stratified by Age											
Age 20-40											
Education	-0.14 (-0.18, -0.11)	-0.08 (-0.09, -0.06)	-0.03 (-0.04, -0.01)	-0.07 (-0.09, -0.06)	-0.04 (-0.05, -0.02)	-0.05 (-0.06, -0.03)	-0.07 (-0.08, -0.05)	-0.06 (-0.08, -0.05)	-0.02 (-0.04, -0.01)	-0.06 (-0.08, -0.04)	-0.07 (-0.09, -0.06)
Annual income	-0.09 (-0.12, -0.06)	-0.06 (-0.08, -0.05)	0.001 (-0.01, 0.02)	-0.06 (-0.08, -0.04)	-0.03 (-0.04, -0.01)	-0.04 (-0.06, -0.03)	-0.04 (-0.06, -0.03)	-0.04 (-0.06, -0.03)	-0.004 (-0.02, 0.01)	-0.05 (-0.07, -0.03)	-0.05 (-0.06, -0.03)
Poverty ratio	-0.13 (-0.16, -0.1)	-0.1 (-0.11, -0.08)	-0.02 (-0.04, -0.005)	-0.07 (-0.09, -0.05)	-0.004 (-0.02, 0.01)	-0.04 (-0.05, -0.02)	-0.03 (-0.05, -0.02)	-0.05 (-0.07, -0.04)	-0.01 (-0.02, 0.01)	-0.04 (-0.05, -0.02)	-0.05 (-0.07, -0.04)
Age 40-60											
Education	-0.2 (-0.24, -0.17)	-0.09 (-0.1, -0.07)	-0.1 (-0.11, -0.08)	-0.1 (-0.12, -0.08)	-0.11 (-0.13, -0.09)	-0.08 (-0.09, -0.06)	-0.08 (-0.09, -0.06)	-0.11 (-0.12, -0.09)	-0.08 (-0.1, -0.07)	-0.09 (-0.11, -0.07)	-0.13 (-0.14, -0.11)
Annual income	-0.19 (-0.23, -0.16)	-0.15 (-0.17, -0.13)	-0.09 (-0.11, -0.07)	-0.17 (-0.19, -0.15)	-0.14 (-0.15, -0.12)	-0.13 (-0.14, -0.11)	-0.13 (-0.15, -0.11)	-0.14 (-0.16, -0.12)	-0.09 (-0.11, -0.08)	-0.16 (-0.18, -0.14)	-0.15 (-0.17, -0.13)
Poverty ratio	-0.2 (-0.23, -0.16)	-0.17 (-0.18, -0.15)	-0.08 (-0.1, -0.07)	-0.15 (-0.17, -0.13)	-0.12 (-0.13, -0.1)	-0.11 (-0.12, -0.09)	-0.11 (-0.12, -0.09)	-0.14 (-0.16, -0.12)	-0.08 (-0.09, -0.06)	-0.13 (-0.15, -0.11)	-0.14 (-0.16, -0.13)
Age 60-80											
Education	-0.24 (-0.28, -0.2)	-0.07 (-0.09, -0.05)	-0.1 (-0.13, -0.08)	-0.12 (-0.14, -0.1)	-0.12 (-0.14, -0.1)	-0.07 (-0.09, -0.05)	-0.06 (-0.08, -0.04)	-0.1 (-0.12, -0.08)	-0.09 (-0.11, -0.07)	-0.09 (-0.11, -0.07)	-0.12 (-0.14, -0.1)
Annual income	-0.24 (-0.29, -0.19)	-0.1 (-0.12, -0.08)	-0.12 (-0.14, -0.1)	-0.15 (-0.18, -0.13)	-0.16 (-0.18, -0.14)	-0.11 (-0.13, -0.09)	-0.11 (-0.13, -0.08)	-0.12 (-0.14, -0.1)	-0.11 (-0.14, -0.09)	-0.13 (-0.15, -0.11)	-0.14 (-0.16, -0.12)
Poverty ratio	-0.25 (-0.3, -0.21)	-0.14 (-0.16, -0.12)	-0.13 (-0.16, -0.11)	-0.17 (-0.19, -0.15)	-0.16 (-0.18, -0.14)	-0.12 (-0.14, -0.09)	-0.11 (-0.13, -0.08)	-0.14 (-0.17, -0.12)	-0.12 (-0.14, -0.09)	-0.14 (-0.16, -0.11)	-0.16 (-0.18, -0.14)

KDM = Klemera-Doubal method, HD = homeostatic dysregulation, CI = confidence interval. Coefficients are from linear regressions of biological aging measures on measures of socioeconomic circumstances. KDM and PhenoAge measures were differenced from chronological age for analysis (i.e. values = BA-CA). These differenced values were then standardized to have M=0, SD=1 separately for men and women within the analysis sample. Socioeconomic circumstances measures were standardized to M=0, SD=1 for analysis so that effect-sizes are denominated in terms of a 1 SD unit improvement in socioeconomic circumstances. Models included covariates for chronological age and sex. The original KDM algorithm (left-most column) was projected onto data from NHANES 2007-2010 only because other NHANES IV waves did not include spirometry measurements. The original PhenoAge algorithm (second column from left) was projected onto data from NHANES 1999-2010 and 2015-2018 only because the intervening waves did not include CRP measurements

II. Analysis of the CALERIE data using the BioAge package

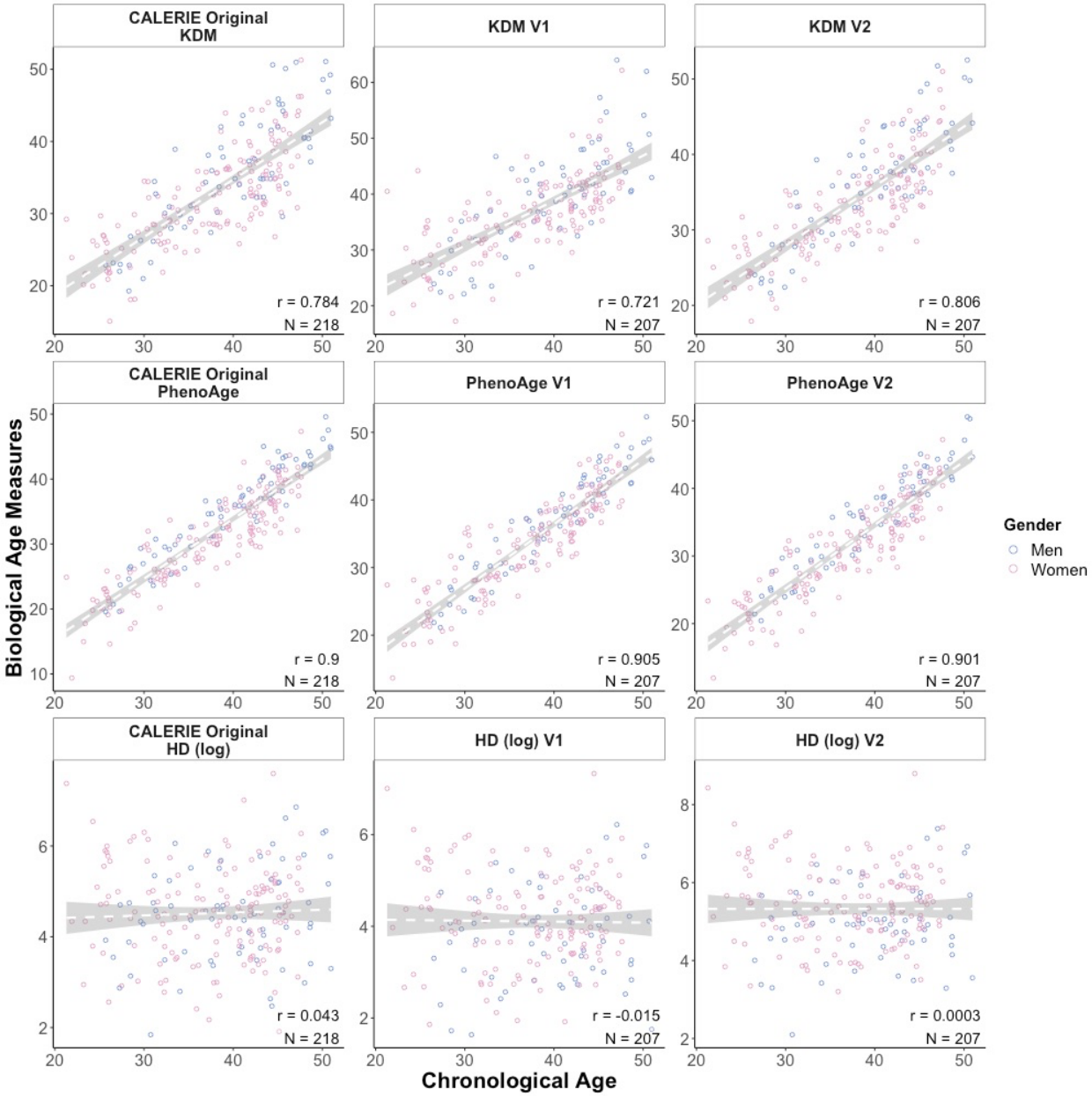


Fig s2.1 KDM, PhenoAge, and HD biological aging measures plotted against chronological age for participants in the CALERIE

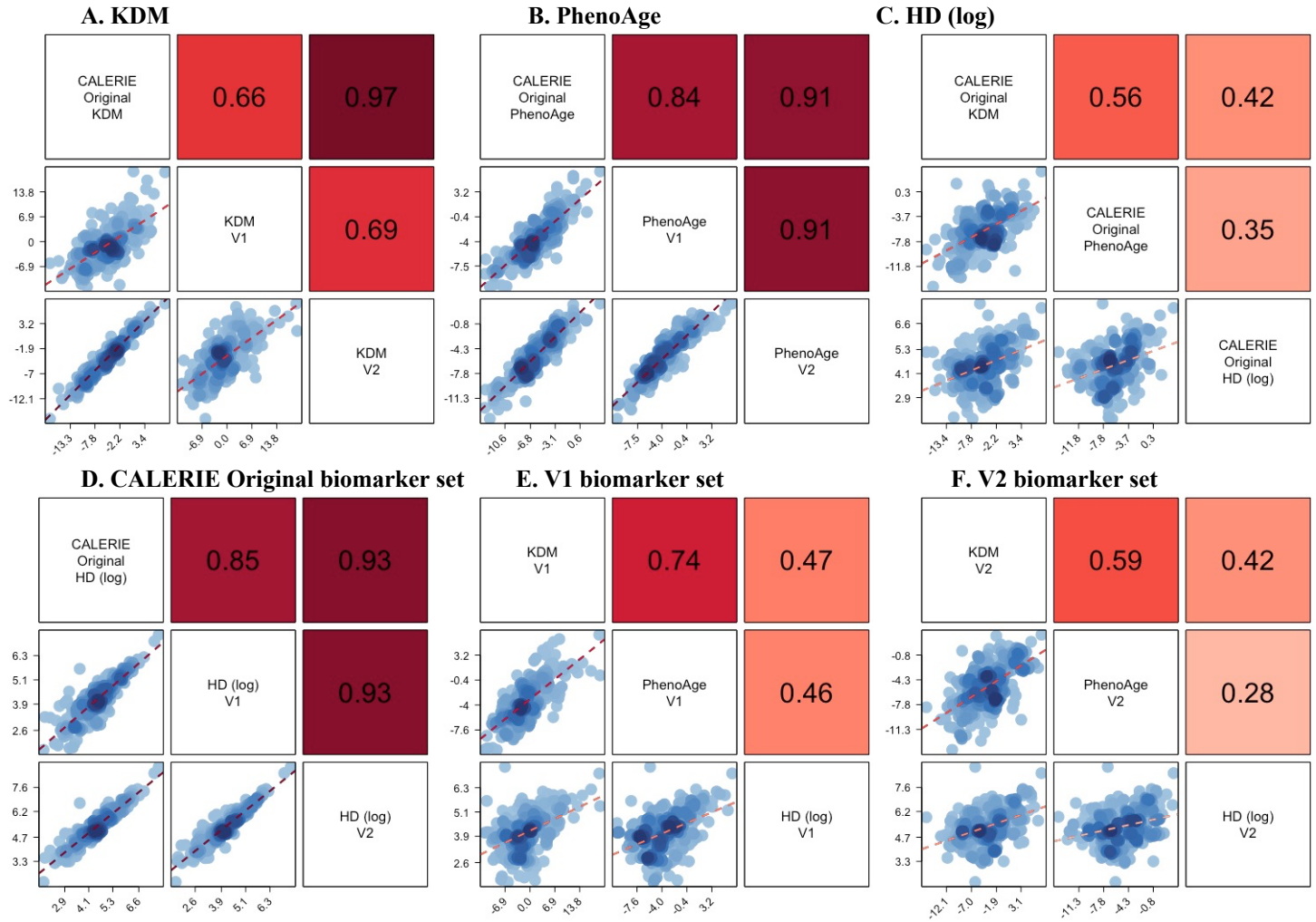


Fig s2.2 A matrix of association plots among KDM, PhenoAge, and HD biological aging measures in the CALERIE

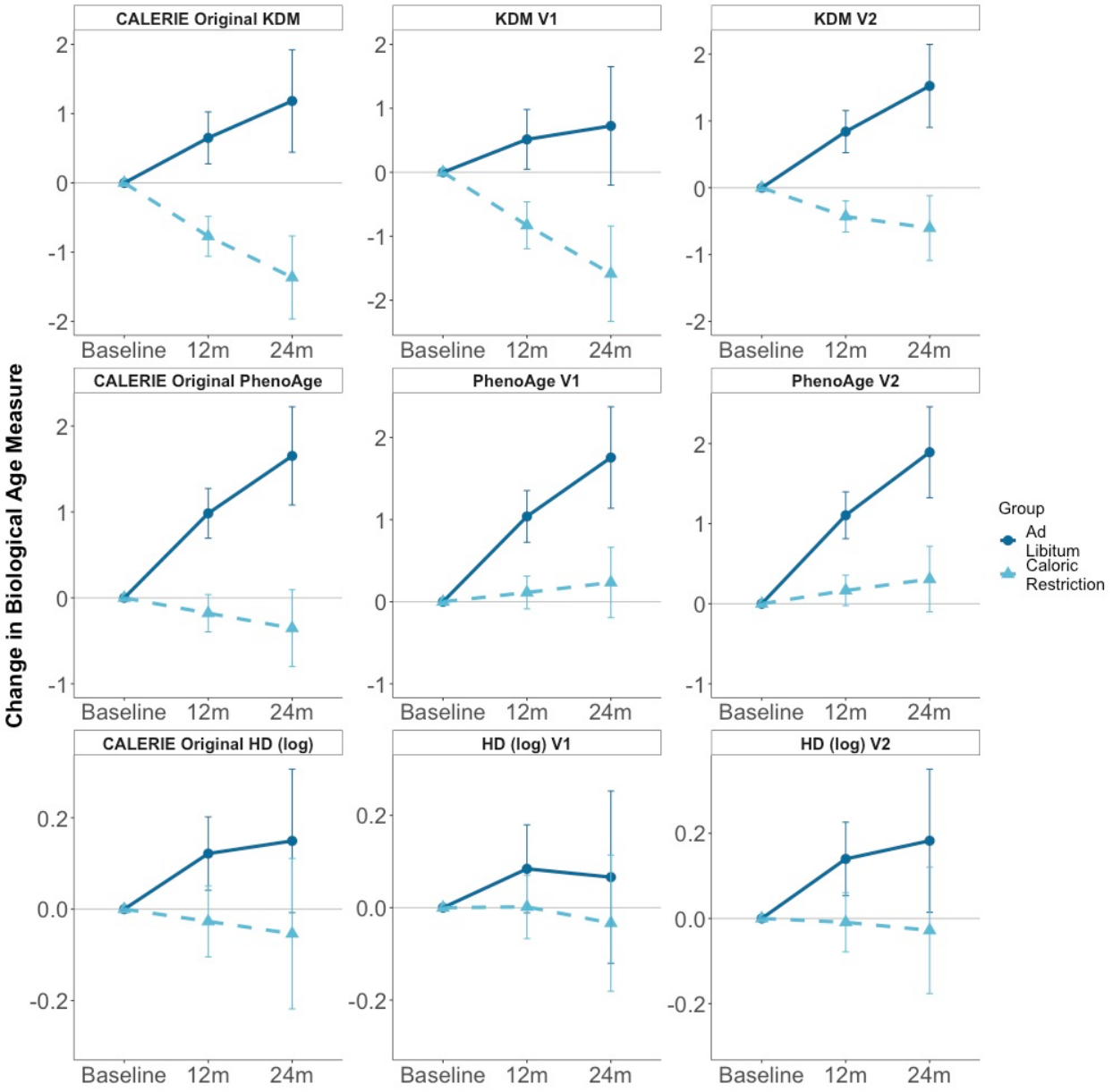


Fig s2.3 Change in KDM, PhenoAge, and HD biological aging measures from Baseline to 12- and 24-month follow-ups in the ad libitum (dark blue dots) and caloric-restriction (light blue triangles) arms of the CALERIE trial. Mean values with 95% confidence intervals were calculated for each follow-up

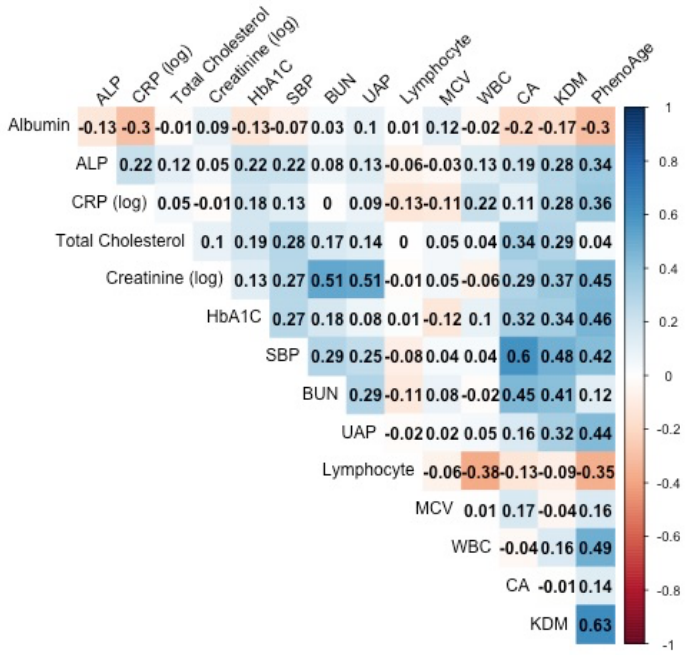
Tab s2.1 Parameters used to calculate biological aging measures in the CALRIE dataset. The "CALERIE Original" biomarker set was composed based on the original set of biomarkers used by Levine in KDM-Biological Age analysis [1]. The original KDM-Biological Age biomarker set was itself defined based on testing correlations of biomarkers with chronological age in the NHANES dataset. Of these biomarkers, lung function and cytomegalovirus infection biomarkers were not available in the CALERIE Dataset and uric acid and white blood cell count were substituted [2]. The V1 biomarker set used in the original PhenoAge algorithm was defined based on elastic net regression of mortality on 42 blood chemistry and complete-blood-count biomarkers and chronological age in the NHANES III dataset.

Panel A. Biomarker sets used to calculate the biological aging measures

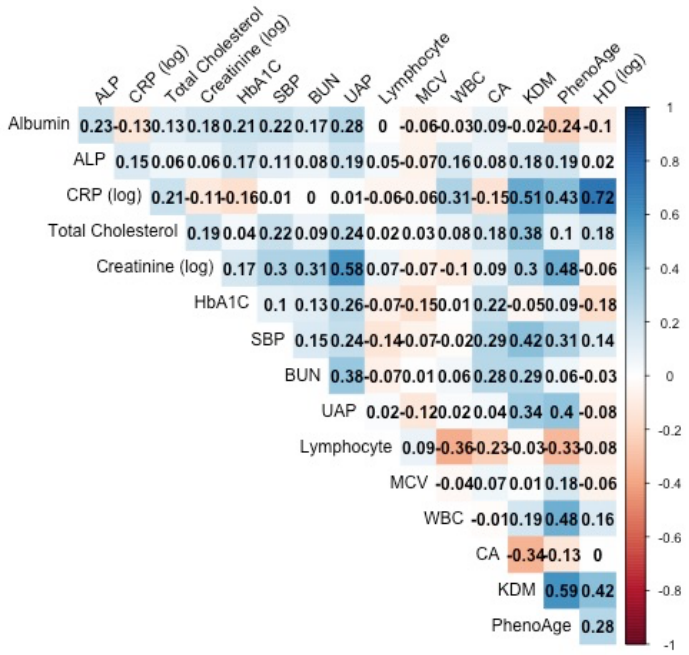
	Biomarker Set		
	CALERIE Original	**V1**	**V2**
Biomarkers included in NHANES III Training Analysis			
Albumin	X	X	X
Alkaline Phosphatase	X	X	X
Blood Urea Nitrogen (BUN)	X		X
Creatinine	X	X	X
C-reactive Protein (CRP)	X	X	X
Glucose		X	
Glycated Hemoglobin (HbA1C)	X		X
Lymphocyte %		X	X
Mean Cell Volume (MCV)		X	X
Red Cell Distribution Width (RDW)			
Systolic Blood Pressure (SBP)	X		X
Total Cholesterol	X		X
Uric Acid	X		X
White Blood Cell Count (WBC)	X	X	X
Correlation with Chronological Age in NHANES IV			
KDM	0.92	0.90	0.94
PhenoAge	0.97	0.97	0.97
HD (log)	0.35	0.28	0.50
Correlation with Chronological Age in CALERIE			
KDM	0.78	0.72	0.81
PhenoAge	0.90	0.91	0.90
HD (log)	0.04	-0.02	0.00

Panel B. The NHANESIII (A) and CALERIE baseline (B) correlation matrices for the V2 biomarker sets. The correlation matrices include the set of biomarkers used to compose the V2 biological age algorithms, chronological age, the V2 biological age advance measures, and V2 homeostatic dysregulation. Biomarker abbreviations are as follows: ALP – alkaline phosphatase, CRP – C-reactive protein, HbA1C – glycated hemoglobin, SBP – systolic blood pressure, BUN – blood urea nitrogen, UAP – uric acid, MCV – mean cell volume, WBC – white blood cell count, CA – chronological age. Biological age advance values were computed by taking the difference of each of KDM Biological Age and PhenoAge from chronological age

A. NHANESIII



B. CALERIE baseline



Tab s2.2 Summary statistics of biological aging measures in the CALERIE baseline

Biomarker set	n	Mean	SD
Chronological age	220	38.10	7.18
CALERIE Original			
KDM	218	33.25	7.28
PhenoAge	218	32.19	7.33
HD (log)	218	4.52	1.03
V1			
KDM	207	37.17	7.95
PhenoAge	207	34.46	7.47
HD (log)	207	4.11	1.03
V2			
KDM	207	34.17	6.96
PhenoAge	207	32.64	7.42
HD (log)	207	5.32	1.04

Tab s2.3 Estimated annual change in KDM, PhenoAge, and HD biological aging measures from baseline through 24-month follow-up in Ad libitum- and Caloric Restriction-arm Participants in the CALERIE Randomized Trial

Biomarker Set		b	[95% CI]	p value	n
CALERIE Original					
KDM	Ad libitum	0.52	[0, 1.05]	0.053	73
	Caloric restriction	-0.54	[-0.92, -0.15]	0.007	145
	Interaction	-1.06	[-1.71, -0.41]	0.002	218
PhenoAge	Ad libitum	0.71	[0.34, 1.09]	<0.01	73
	Caloric restriction	-0.11	[-0.39, 0.16]	0.422	145
	Interaction	-0.83	[-1.29, -0.36]	0.001	218
HD (log)	Ad libitum	0.05	[-0.08, 0.18]	0.447	73
	Caloric restriction	-0.02	[-0.12, 0.08]	0.658	145
	Interaction	-0.07	[-0.24, 0.09]	0.382	218
V1					
KDM	Ad libitum	0.24	[-0.44, 0.93]	0.487	68
	Caloric restriction	-0.66	[-1.16, -0.16]	0.01	139
	Interaction	-0.9	[-1.75, -0.06]	0.037	207
PhenoAge	Ad libitum	0.77	[0.38, 1.17]	<0.01	68
	Caloric restriction	0.13	[-0.15, 0.42]	0.372	139
	Interaction	-0.64	[-1.13, -0.16]	0.01	207
HD (log)	Ad libitum	0	[-0.14, 0.14]	0.987	68
	Caloric restriction	-0.02	[-0.12, 0.08]	0.72	139
	Interaction	-0.02	[-0.19, 0.15]	0.823	207
V2					
KDM	Ad libitum	0.69	[0.21, 1.16]	0.005	68
	Caloric restriction	-0.2	[-0.55, 0.14]	0.248	139
	Interaction	-0.89	[-1.47, -0.31]	0.003	207
PhenoAge	Ad libitum	0.83	[0.46, 1.21]	<0.01	68
	Caloric restriction	0.17	[-0.11, 0.44]	0.232	139
	Interaction	-0.67	[-1.13, -0.2]	0.006	207
HD (log)	Ad libitum	0.06	[-0.08, 0.2]	0.411	68
	Caloric restriction	-0.01	[-0.12, 0.09]	0.784	139
	Interaction	-0.07	[-0.25, 0.1]	0.409	207

The regression model included sex and age at baseline as covariates. CI = Confidence interval

References

1. Levine ME. Modeling the Rate of Senescence: Can Estimated Biological Age Predict Mortality More Accurately Than Chronological Age? J Gerontol a-Biol. 2013 Jun;68(6):667-74. PMID: WOS:000319466000005. doi: 10.1093/gerona/gls233.
2. Belsky DW, Caspi A, Cohen HJ, Kraus WE, Ramrakha S, Poulton R, et al. Impact of early personal-history characteristics on the Pace of Aging: implications for clinical trials of therapies to slow aging and extend healthspan. Aging Cell. 2017 Aug;16(4):644-51. PMID: 28401731. doi: 10.1111/acel.12591.